REMARKS

Claims 1-4, 6, 8, 10-16, 19-21, 23-24, 26, 29-40, 43-53, 56-73, 76-97, 100-12, 114-125, and 128-138 are pending in the present application. Claims 5, 7, 9, 17-18, 22, and 25 were previously canceled. Claims 27-28, 41-42, 54-55, 74-75, 98-99, 113, and 126-127 have been canceled herein without prejudice or disclaimer. Claims 10-11, 34-35, 45-53, 56-73, 76-97, 100-111, 115-117, 129-130, and 134 have been withdrawn from consideration as being drawn to a non-elected invention. Applicants thank the Examiner for conducting an Examiner interview with the undersigned attorney and Susanne Hopkins on October 16, 2007.

The specification has been amended at paragraphs [0014] and [0032] to correct minor typographical errors. No new matter has been added.

Claims 27-28, 41-42, 54-55, 74-75, 98-99, 113, and 126-127 have been canceled without prejudice or disclaimer and claims 1-3, 20-21, 24, 30, 32, 43-45, 49, 56, 61, 65-70, 76, 79, 81, 88-93, 100, 103, 105, 111-117, 119, 128, 133, and 138 have been amended, for the sole reason of advancing prosecution. Applicants, by canceling or amending any claims, make no admission as to the validity of any rejection made by the Examiner against any of these claims. Applicants reserve the right to reassert any of the claims canceled herein or the original claim scope of any claim amended herein, in a continuing application.

Claims 1, 21, 30, 45, 66, 89, and 112 have been amended to recite "...wherein when the co-solvent comprises one or more polyhydric alcohols, the one

or more polyhydric alcohols are present in an amount of less than 10% by weight...." Support for this amendment appears throughout the specification and claims as originally filed.

Claims 1, 21, 30, 45, 66, 89, and 112 have also been amended to recite "...in a solvent of water and a lower alcohol wherein the ratio of water to alcohol is in a range of approximately 9:1 to 1:9 by volume." Support for this amendment appears throughout the specification and claims as originally filed.

Claim 112 has been amended to incorporate the penetration enhancers recited in claim 113 now canceled.

Claims 21, 44, 65, 88, 111, and 138 have been amended to delete the language "prophylactically effective amount."

Claims 1, 3, 20, 24, 30, 49, 68, 91, and 119 have been amended to replace the term "approximately 5%" with the term "at least 5%." Support for this amendment appears throughout the specification and claims as originally filed.

In addition, claims 2,14, 24, 32, 61, 67-70, 79, 81, 88, 90-93, 103, 105, 113-117, 133, and 138 have been amended to correct minor typographical and grammatical errors.

Support for the foregoing amendments appears throughout the specification and claims as originally filed. No new matter has been added.

The following are submitted herewith: (i) a Declaration under 37 CFR § 1.132 by Barry Hunt; (ii) a copy of a Declaration submitted in corresponding US Patent Application No. 10/124,197 now US Patent No. 6,946,120 by Albert Zorko Abram with attachments; and (iii) *Skin Permeation, Fundamentals and Application*, Joel L. Zatz, PhD, pp. 28-29.

In view of the following, further and favorable consideration is respectfully requested.

I. At page 3 of the final Official Action, claims 1-3, 6, 8, 12, 13, 15-16, 19-21, 23-24, 26-29, 112-114, 118-119, 121-128, 131-132, and 135-138, have been rejected under 35 USC § 103 (a), as being unpatentable over Peck et al. in view of Weiner et al. or Yu et al., respectively.

The Examiner asserts that "Peck et al. teaches a quick breaking foam to treat alopecia comprising (a) 1-5% minoxidil; (b) 10-50% propylene glycol; (c) 30-75% alcohol; (d) 0.5-10% emulsifier and/or surfactant; (e) 0.1-5% hydroxypropyl methylcellulose; and (f) 10-50% water, wherein the composition is actuated with a propellant." The Examiner states that "Peck does not teach the instant acid salt." The Examiner concludes that "[i]t would have been obvious to the skilled artisan to combine the teachings of Peck et al. and Weiner and utilize the instant minoxidil acid salt" because Weiner teaches that this addition yields a hydrophilic compound that allows for better penetration into the hair follicles.

With regard to Weiner et al. the Examiner also asserts that Weiner et al. teaches "modifying the solubility of the active in an aqueous solution by making it

more hydrophilic without changing the active agent's therapeutic properties" and that "the active agent that is more hydrophilic, has improved penetration through the hair follicle." The Examiner points to Weiner et al. at pages 3 and 4 in support of her position.

In view of the following, this rejection is respectfully traversed. Claims 27-28, 113, and 126-127 have been canceled without prejudice or disclaimer, rendering this rejection moot with respect to these claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity

will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined, must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

Regarding *teaching away*, **MPEP 2141.02** states that prior art must be considered in its entirety, including disclosures that *teach away* from the claims. See also **MPEP 2145(X)(D)**. The Federal Circuit in *Takeda v. Alphapharm* found

that the prior art taught away from the closest compound because the prior art in fact disclosed a broad selection of compounds where the closest prior art compound exhibited negative properties that would have led the skilled artisan away from that compound.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* Federal Circuit, No. 06-1325 (June 28, 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The district court considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The district court found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

It is submitted that a *prima facie* case of obviousness has not been established because the Peck et al. and Weiner et al. references or the Peck and Yu et al. references fail to teach or suggest all of the limitations of the claims as required by *In re Wilson*. Further, a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Peck et

al. to incorporate the acid salt of Weiner et al. since Weiner et al. teaches away from a minoxidil acid salt.

Claims 1, 21, and 112 have been amended to recite that "... when the co-solvent comprises one or more polyhydric alcohols, the one or more polyhydric alcohols are present in an amount of less than 10% by weight." Accordingly, all of the rejected claims recite polyhydric alcohol present in an amount of less than 10% by weight. In addition, claims 1 and 112 recite the transition language "consisting essentially of." Claim 21 recites providing a pharmaceutical composition "consisting essentially of." This transition language excludes components that materially affect the claimed product or process. More specifically, with regard to the present claims, the transition language "consisting essentially of" excludes encapsulation in lipid vesicles.

The Peck et al. and Weiner et al. references, or the Peck et al. and Yu et al. references, fail to teach or suggest all of the limitations of the claims as required by *In re Wilson*, because none of the foregoing references taken alone or together, teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight polyhydric alcohol, as is presently claimed.

Peck et al. broadly describes at page 2, composition (1) that includes 1 to about 5% minoxidil and 10 to about 50% propylene glycol. Thereafter, Peck et al. describes specific formulations, for example, formulations (e) and (f) at page 4, that

each include 50% propylene glycol and 5% minoxidil. Further, each of Examples 5 and 6 of Peck et al. describe preparing compositions including 5% minoxidil and 50% propylene glycol.

Peck et al. ***teaches away*** from the presently claimed subject matter, because the formulations of Peck et al. that include a high concentration of minoxidil, i.e. 5%, also include high concentrations of propylene glycol, i.e., 50%. *See* formulations (e) and (f), and Examples 5 and 6, of Peck et al. Numerous other prior art formulations also teach away from the present invention by requiring high percentages of propylene glycol or a similar diol or triol to achieve high minoxidil concentrations, i.e. greater than 5% (see the present specification at page 1, lines 11-21). **Thus, no suggestion or motivation has been provided to modify Peck et al. to arrive at the composition as recited in the present claims.**

Moreover, all of the examples of Peck et al. have very ***high levels*** of propylene glycol or other diols and triols. This is conventional technology that uses high propylene glycol concentrations in order to load minoxidil into the formulation. In Example 1, where the propylene glycol amount is 20%, there is only 2% minoxidil in the formulation. In Example 2(a), where propylene glycol and butylene glycol are present in a combined amount of 40%, there is only 2% minoxidil. In Example 2 (b), where the butylene glycol amount is 15%, there is only 1% minoxidil. Likewise, in Examples 3 and 4, where the propylene glycol amount is 30%, there is only 2% minoxidil in the formulation. In Example 7, where propylene glycol and butylene

glycol are present in a combined amount of 25%, there is only 2% minoxidil. Only in Examples 5 and 6 where the propylene glycol amount is 50%, is minoxidil present in an amount of 5% in the formulations. This does not teach or suggest an advantage of having ***BOTH* reduced levels** of the co-solvent such as less than 10% polyhydric alcohol and **high loading of minoxidil** such as at least 5%, as presently claimed. Accordingly, Peck et al. does not teach or suggest the presently claimed subject matter.

The foregoing remarks are further supported by the Declaration under 37 CFR §1.132 by Barry Hunt ("the Hunt Declaration") submitted herewith. Barry Hunt is a formulation scientist of the assignee of the subject application and has been in pharmaceutical research since 1972. He has been employed doing formulation research and development for the last 35 years.

In paragraphs 4-8, Mr. Hunt declares that he has reviewed Peck et al. and as exemplified therein, formulations having high loading of minoxidil are accompanied by high levels of polyhydric alcohols. In fact, in paragraph 8, Mr. Hunt sets forth that Peck et al. exemplifies the following formulations:

- The composition of Example 5 contains 5% minoxidil and 50% propylene glycol.
- The composition of Example 6 contains 5% minoxidil and 50% propylene glycol.

- Compositions (e) and (f) each contain 5.0% minoxidil and 50.0% propylene glycol.

- The compositions of claims 13 and 14 each contain 5.0% minoxidil and 50.0% propylene glycol

Thus, Mr. Hunt declares in paragraph 8 that, similar to other compositions described in the prior art, the compositions exemplified in Peck et al. contain a very high percentage (i.e., 50%) of the polyhydric alcohol propylene glycol in order to improve the solubility of a high concentration (i.e. 5%) of minoxidil. Such high amounts of polyhydric alcohol are not pharmaceutically or cosmetically elegant, may be unacceptable to the consumer, and may cause local irritation and hypersensitivity upon application to the scalp (see paragraph 6 of the Hunt Declaration).

With regard to Weiner et al., Weiner et al. does not cure the deficiencies of Peck et al. because Weiner et al. also does not teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight polyhydric alcohol. Weiner et al. describes a formulation that requires minoxidil to be reacted with an acid or base and then be encapsulated into lipid vesicles. *See* page 4, lines 13-18.

Further, the skilled artisan would have no motivation to modify Peck et al. by utilizing the minoxidil acid salt of Weiner et al.

In this regard, the Examiner has asserted that Weiner et al. teaches modifying the solubility of the active in an aqueous solution to make it more hydrophilic does not change the active agent's therapeutic properties, and that the modified active agent (that is more hydrophilic) has improved penetration through the hair follicle. Contrary to the Examiner's assertion, the data presented in Weiner et al. clearly illustrates that changing the solubility of minoxidil by reacting it with an acid renders the resultant formulation ***essentially undeliverable*** in the absence of encapsulation. Accordingly, not only does Weiner et al. illustrate that the resultant unencapsulated formulation does ***not*** exhibit improved penetration through the hair follicle, Weiner et al. clearly illustrates that it exhibits ***extremely poor*** penetration.

Specifically, the data presented in Example 3 of Weiner et al. shows that minoxidil reacted with lactic acid (formulation **XI**), but not encapsulated in a lipid vesicle, is essentially undeliverable into hairless rat skin. In contrast, the Weiner et al. data shows that a lipid vesicle encapsulated lactic acid-treated minoxidil (formulation **III**) penetrated living skin strata more deeply than the other tested formulations. *See* formulations **III** and **XI** in Table 1, on page 6, in the "Living skin Strata" column, and page 7, lines 9-17.

As can be seen from Table 1 of Weiner et al., the percentage of the applied dose of encapsulated minoxidil salt formulation **III** that penetrated the living skin strata was 0.75±0.33 while the percentage of unencapsulated minoxidil salt formulation **XI** that penetrated the living skin strata was 0.18±0.01. Applicants note

Weiner et al. states at page 7, line 3, that "Formula **XI** is the same as Formula **III** except lacking the vesicles." This data clearly shows that encapsulated minoxidil lactic acid salt formulation **III** had more than four times the penetration into the deepest skin strata than that of unencapsulated minoxidil lactic acid salt formulation **XI**.

Further, contrary to the Examiners assertion, Weiner et al. attributes improved penetration of the encapsulated minoxidil formulation to the lipid vesicle and the particular lipid selected and ***not*** to the minoxidil acid salt. Specifically, Weiner et al. states at page 7, lines 15-17, that "[W]hat is most interesting is that a simple change from glycerol dilaurate (C12) to glycerol disterate (C18) in the vesicle wall changes the penetration several fold."

In view of the foregoing, the skilled artisan would have no motivation to prepare a formulation by reacting minoxidil with an acid, absent encapsulation of the resultant minoxidil acid salt in a lipid vesicle, because Weiner et al. describes that ***an unencapsulated minoxidil salt formulation exhibits less than one-quarter the penetration exhibited by an encapsulated minoxidil acid salt formulation.***

Again, claims 1 and 112 recite the transition language "consisting essentially of." Claim 21 recites providing a pharmaceutical composition "consisting essentially of." This transition language excludes components that materially affect the claimed product or process. More specifically, with regard to the present claims, the

transition language "consisting essentially of" excludes encapsulation in lipid vesicles.

In addition, Weiner et al. ***teaches away*** from preparing an unencapsulated minoxidil acid salt formulation, because the skilled artisan in view of the data in Example 3 would be led away from preparing and administering an unencapsulated minoxidil salt formulation. Specifically, Example 3 of Weiner et al. illustrates that commercial Rogaine® (formulation **XII**), which does not include a minoxidil salt, but includes minoxidil in a combination of ethanol, propylene glycol and water and is not encapsulated in a lipid vesicle, was second only to formulation **III** in efficacy (penetration of living skin strata). Again, Weiner et al. describes that the percentage of unencapsulated minoxidil salt formulation **XI** that penetrated the living skin strata was 0.18±0.01. The percentage of unencapsulated minoxidil formulation **XII** that penetrated the living skin strata was 0.35±0.14. This data clearly shows that unencapsulated minoxidil formulation **XII** had ***twice*** the penetration into the deepest skin strata than that of unencapsulated minoxidil lactic acid salt formulation **XI**. Thus, the skilled artisan in view of the data in Weiner et al., which shows that unencapsulated minoxidil formulation **XII** (commercial Rogaine®) exhibits significantly greater penetration than unencapsulated minoxidil lactic acid salt formulation **XI**, would be ***led away*** from preparing an unencapsulated minoxidil salt formulation.

In view of the foregoing, the skilled artisan would have had no motivation to prepare a formulation employing a minoxidil salt or by reacting minoxidil with an acid to form a minoxidil salt. Weiner et al. illustrates that an unencapsulated minoxidil salt formulation exhibits only half the penetration exhibited by an unencapsulated minoxidil propylene glycol formulation (commercial Rogaine®) and thus ***teaches away*** from the present claims.

In further support of the above, Applicants submit that increasing solubility is not equivalent to increasing skin permeation. Please see pages 28-29 of *Skin Permeation, Fundamentals and Application*, Joel L. Zatz, PhD, attached hereto. More specifically, page 29, lines 2-4, describe that "In every case studied, the permeability coefficient of the unionized form exceeds that of the charged species, in some cases by two or three orders of magnitude."

With regard to Yu et al., Yu et al. does not cure the deficiencies of Peck et al. because Yu et al also does not teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than approximately 10% by weight polyhydric alcohol. Yu et al. is directed to the use of hydroxyacids to enhance the "therapeutic efficacy of cosmetic and pharmaceutical agents." *See* col. 2, lines 16-21. In particular, Yu et al. describes the use of "hydroxycarboxylic acids and related compounds" as "enhancing compounds" to

enhance the therapeutic efficacy of cosmetic and pharmaceutical agents in topical treatment of cosmetic conditions, dermatologic disorders, or other afflictions. *See* col. 2, lines 16-42.

Yu et al. is not concerned with and does not even remotely address the problem that the present invention solves, namely, increasing minoxidil amounts while minimizing amounts of propylene glycol, or other polyols. Yu et al. clearly does not describe or suggest the present composition which requires "at least 5% by weight, based on the total weight of the composition, of minoxidil or a pharmaceutically acceptable salt thereof," "an acid in an amount to substantially completely solubilize the minoxidil or a pharmaceutically acceptable salt thereof," and a co-solvent wherein when the co-solvent comprises one or more polyhydric alcohols, the one or more polyhydric alcohols are present in an amount of "less than 10% by weight."

Example 3 of Yu et al. describes a "2% minoxidil" formulation formed by dissolving 2 grams minoxidil and 3 ml lactic acid into a mixture of 80 ml ethanol and 15 ml propylene glycol. A 2% minoxidil formulation contains much less minoxidil that the present compositions which require at least 5% minoxidil. In addition, the formulation of Example 3 of Yu et al. has a large propylene glycol content, i.e., 15%, which amount is substantially greater than the presently claimed "less than 10% by weight."

In addition, Applicants submit that any suggestion in Yu et al. to employ a minoxidil acid salt is negated by the disclosure of Weiner et al. in view of the more exhaustive and reliable scientific analysis presented by Weiner et al. and the teaching away from the present claims by Weiner et al. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., Id.*

More specifically, Weiner et al. in Examples 1-3 and in Tables 1 and 2, at pages 4-8, provides extensive comparative penetration data with regard to various encapsulated and unencapsulated minoxidil formulations. Further, as discussed herein, Weiner et al. teaches away from the use of an unencapsulated minoxidil salt formulation. On the other hand, Yu et al. provides no data at all with regard to minoxidil formulations. Only ***prophetic*** Example 3 of Yu et al. is directed to a composition containing a minoxidil acid salt. No data is provided. Accordingly, Weiner et al. is entitled to more weight than Yu et al. in accordance with *Takeda*.

In view of the foregoing, it is submitted that nothing in Peck et al., Weiner et al., and Yu et al., taken alone or together, renders the claimed invention obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-3, 6, 8, 12, 13, 15-16, 19-21, 23-24, 26, 29, 112, 114, 118-119, 121-125, 128, 131-132, and 135-138.

II. At page 4 of the Official Action, claims 14, 30-33, 36-44, and 133, have been rejected under 35 USC § 103 (a), as being unpatentable over Peck et al. in view of Weiner et al. or Yu et al., respectively, and further in view of Uchikawa et al.

The Examiner asserts that it would have been obvious to the skilled artisan "to combine the teachings of the above references and substitute the exemplified propylene glycol with the instantly claimed glycerol and arrive at the instant invention" because "Uchikawa et al. teaches both propylene glycol and glycerol are polyhydric alcohols conventionally used in the art."

In view of the following, this rejection is respectfully traversed.

Claims 41 and 42 have been canceled without prejudice or disclaimer, rendering this rejection moot with respect to these claims.

As discussed above, none of Peck et al., Weiner et al. or Yu et al., taken alone or together, teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight polyhydric alcohol, as presently claimed.

In addition, Weiner et al. ***teaches away*** from preparing an unencapsulated minoxidil salt formulation. Please *see* the above discussions in Section I, regarding Peck et al., Weiner et al. and Yu et al., as well as the Hunt Declaration, which arguments are hereby incorporated by reference in their entirety.

Again, Applicants submit that any suggestion in Yu et al. to employ a minoxidil acid salt, is negated by the disclosure of Weiner et al. in view of the more exhaustive and reliable scientific analysis presented by Weiner et al. and the

teaching away from the present claims by Weiner et al. *See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., Id.*

Applicants submit that Uchikawa et al. does not cure the deficiencies of Peck et al., Weiner et al., and/or Yu et al., because Uchikawa et al. does not teach or suggest a composition having ***BOTH*** at least 5% minoxidil or a pharmaceutically acceptable salt thereof ***AND*** less than 10% by weight polyhydric alcohol, as presently claimed. Further, Uchikawa et al. does not teach or suggest employing a minoxidil acid salt.

In view of the foregoing, it is submitted that nothing in the applied references, taken alone or together, render the claimed invention obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 14, 30-33, 36-40, 43-44, and 133.

III. At page 5 of the Official Action, claims 1-4, 6, 8, 12-13, 15-16, 20-21, 23-24, 26-31, 36-37, 39-44, 112-113, 118-128, 131-132, 135-136, and 138, have been rejected under 35 USC § 103 (a), as being unpatentable over Di Schiena in view of Yu et al.

The Examiner asserts that "it would have been obvious to one or ordinary skill in the art at the time the invention was made to combine the teachings of Di Schiena and Yu et al. and add a hydroxyl acid such as lactic acid to the composition" because Yu et al. "teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil."

In response to Applicants arguments, the Examiner states that "Di Schiena teaches reacting oxyniacic acid and minoxidil to form the compound of formula I, i.e. a minoxidil salt, which reads on the present "pharmaceutically acceptable salt" of minoxidil." With regard to the Declaration filed on May 22, 2006, the Examiner asserts that the "Declaration under 37 CFR 1,132 filed 5/22/06 is insufficient to overcome the rejection" because "the claims are not commensurate in scope." The Examiner asserts that "the unexpected property of homogeneity is due to the components in the inventive composition and the ratio used in the Rule 132 Declaration."

In view of the following, this rejection is respectfully traversed.

Claims 27-28, 41-42, 113, and 126-127 have been canceled without prejudice or disclaimer, rendering this rejection moot with respect to these claims.

As discussed during the Examiner interview of October 16, 2007, claims 1, 21, 30, and 112 have been amended to recite "...in a solvent of water and a lower alcohol wherein the ratio of water to alcohol is in a range of approximately 9:1 to 1:9 by volume...." Applicants submit that the amended claims are commensurate in scope with the Declaration filed on May 22, 2006. The Examiner appears to indicate at page 7, lines 1-5 of the subject final Official Action, that those amendments would overcome this rejection.

In view of the foregoing, it is submitted that nothing in any of Di Schiena and Yu et al., taken alone or together, suggests the presently claimed subject matter

within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-4, 6, 8, 12-13, 15-16, 20-21, 23-24, 26, 29-31, 36-37, 39-40, 43-44, 112, 118-125, 128, 131-132, 135-136, and 138.

IV. At page 7 of the Official Action, claims 1-4, 6, 8, 15-16, 19-21, 23-24, and 26-27, have been rejected under 35 USC § 103 (a), as being unpatentable over JP 07-048230 in view of Weiner et al. or Yu et al., respectively, further in view of Caldini et al.

The Examiner asserts that it would have been obvious to the skilled artisan to combine the teachings of JP '230 and Weiner et al. or Yu et al. and utilize the instant minoxidil acid salt. The Examiner further asserts that it would have been obvious to the skilled artisan to combine the teachings of the references and utilize benzyl alcohol in the solvent system because Caldini et al. teaches that the use of benzyl alcohol improves transcutaneous and transfollicular absorption of active agents.

In view of the following, this rejection is respectfully traversed.

Claim 27 has been canceled without prejudice or disclaimer, rendering this rejection moot with respect to this claim.

JP '230 describes a hair tonic including 0.1 to 10 g. minoxidil, 30-70 g. ethanol, and water. JP'230, as admitted by the Examiner, does not teach or suggest adding an acid or a co-solvent.

As discussed above, Weiner et al. teaches away from preparing and/or administering an unencapsulated minoxidil acid salt formulation. The skilled artisan in view of Weiner et al. would have had no motivation to prepare a formulation by employing a minoxidil salt or by reacting minoxidil with an acid to form a minoxidil salt, absent encapsulation of the minoxidil salt in a lipid vesicle because Weiner et al. describes that an unencapsulated minoxidil salt exhibits extremely poor penetration. Further, as discussed above, the skilled artisan would have had no motivation to prepare a formulation employing a minoxidil salt or by reacting minoxidil with an acid to form a minoxidil salt, because Weiner et al. describes that commercial Rogaine® (that is unencapsulated) exhibits significantly greater penetration than exhibited by an unencapsulated minoxidil salt formulation and thus ***teaches away*** from the present claims.

Please *see* the above remarks set forth in Section I, regarding Weiner et al. and Yu et al. incorporated herein by reference in their entirety.

With regard to Yu et al., as discussed above Yu et al. is directed to the use of hydroxyacids to enhance the "therapeutic efficacy of cosmetic and pharmaceutical agents." *See* col. 2, lines 16-21. Again, Yu et al. is not concerned with and does not even remotely address the problem that the presently claimed subject matter solves, namely, increasing minoxidil amounts while minimizing amounts of propylene glycol, or other polyols. Yu et al. clearly does not describe or suggest the present composition which requires "at least 5% by weight, based on the total

weight of the composition, of minoxidil or a pharmaceutically acceptable salt thereof," "an acid in an amount to substantially completely solubilize the minoxidil or a pharmaceutically acceptable salt thereof," and a co-solvent wherein when the co-solvent comprises one or more polyhydric alcohols, the one or more polyhydric alcohols are present in an amount of "less than 10% by weight."

Again, Applicants submit that any suggestion in Yu et al. to employ a minoxidil acid salt, is negated by the disclosure of Weiner et al. in view of the more exhaustive and reliable scientific analysis presented by Weiner et al. and the teaching away from the present claims by Weiner et al.

Prophetic Example 3 of Yu et al. describes a "2% minoxidil" formulation formed by dissolving 2 grams minoxidil and 3 ml lactic acid into a mixture of 80 ml ethanol and 15 ml propylene glycol. A 2% minoxidil formulation contains much less minoxidil than the present compositions which require at least 5% minoxidil. In addition, the formulation of Example 3 of Yu et al. has a large propylene glycol content, i.e., 15%, which amount is substantially greater than the presently claimed "less than 10% by weight."

Regarding Caldini et al., Caldini et al. does not cure the deficiencies of JP 07-048230, Weiner, and Yu et al., taken alone or together, because Caldini et al. does not teach or suggest employing a minoxidil acid salt.

In view of the foregoing, it is submitted that nothing in any of JP 07-048230, Weiner et al., Yu et al., and Caldini et al., taken alone or together, suggests the

presently claimed subject matter within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-4, 6, 8, 15-16, 19-21, 23-24, and 26.

V. At page 8 of the Official Action, claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26-29, 112, 118-128, 131-132, and 135-138, have been rejected under 35 USC § 103 (a), as being unpatentable over Navarro et al. in view of Weiner et al.

The Examiner asserts that it would have been obvious to the skilled artisan "to combine the teachings of Navarro et al. and Weiner et al. and substitute Navarro's cyclodextrin with the instant acid to convert minoxidil into a salt" because "Weiner teaches that by converting minoxidil to a hydrophilic compound, it penetrates the skin."

In response to Applicants arguments, the Examiner asserts that "Weiner teaches modification to active agents including minoxidil includes converting the active to a salt using either an acid such as lactic acid or converting it to a salt by using cyclodextrin" and that "the fact that the converted salt is encapsulated in a liposome later is irrelevant because Weiner et al. teaches the equivalency of modifying minoxidil to a more soluble form by reacting it with cyclodextrin or lactic acid." The Examiner asserts that Applicants "must compare the unexpectedness of using an acid versus cyclodextrin to overcome this rejection." Lastly, the Examiner asserts that, with regard to independent claim 112, the "lipid vesicle of Weiner et al. reads on the penetrating enhancer."

In view of the remarks set forth herein, this rejection is respectfully traversed. Claims 27-28 and 126-127 have been canceled without prejudice or disclaimer, rendering this rejection moot with respect to these claims.

Applicants submit that a proper case of *prima facie* obviousness has not been established because there is no motivation to modify Navarro et al. to incorporate the minoxidil acid salt of Weiner et al.

Navarro et al. describes encapsulating minoxidil in a cyclodextrin carrier, wherein cyclodextrin functions as a "host" molecule to trap the minoxidil "guest" molecule inside the ring. Navarro et al. describes the use of cyclodextrin in order to assist in the solubilization of minoxidil while avoiding high amounts of propylene glycol. Navarro et al. states the following:

> [t]he amount of γ-cyclodextrin present in the composition for hair is such that it permits a substantial reduction in the amount of solvent for minoxidil which would normally need to be added to achieve a comparable solubility of minoxidil in the absence of the aforementioned cyclodextrin. (Page 3, lines 9-13 of the English translation).

From the foregoing, it is clear that cyclodextrin is an essential element of Navarro et al. because it must be combined with minoxidil in order to impart improved solubility properties to minoxidil, thereby reducing the amount of solvent such as propylene glycol needed in the formulation. However, the present claims exclude cyclodextrin by virtue of the transition language "consisting essentially of." As such, the encapsulating technique of Navarro et al. is distinguished.

In further support of the foregoing, submitted herewith is a copy of a Declaration under 37 CFR §1.132 by Albert Zorko Abram ("the Abram Declaration"), filed in corresponding patent application no. 10/124,197 now US Patent No. 6,946,120, in response to a rejection of the pending claims under 35 USC § 103 as obvious in view of the disclosures of Navarro in view of Weiner et al. and further in view of Leitch.

In the Declaration, Mr. Abram declares in paragraph 9 that supplementing the teaching of Navarro with the teaching of Weiner et al. ***would destroy the intended purpose of the Navarro composition***. Mr. Abram declares in paragraph 10 that the role of cyclodextrin in Navarro is to function as a host molecule to trap the minoxidil "guest" molecule inside the ring and that it is the minoxidil-cyclodextrin "host-guest" complex that imparts improved solubility properties, as compared to a similar minoxidil composition not having cyclodextrin. Mr. Abram declares that it is recognized that cyclodextrins are unstable in acidic conditions and that subjecting cyclodextrins to acidic conditions will result in the degradation of the cyclodextrins into its individual glucose units.

Further, as discussed above and contrary to the Examiners assertion, Weiner et al. ***does not*** teach or suggest that converting minoxidil to a hydrophilic compound results in improved penetration through the hair follicle. In fact, the data in Weiner et al. clearly illustrates that a minoxidil salt formulation exhibits markedly poorer penetration as compared to the penetration exhibited by commercial Rogaine®.

Accordingly, Weiner et al. ***teach away*** from the preparation/administration of an unencapsulated minoxidil salt formulation. Please *see* the above discussions in Section I with regard to Weiner et al., incorporated herein by reference in their entirety.

Lastly, with regard to claim 112, claim 112 has been amended to incorporate the penetration enhancers of claim 113. Accordingly, claim 112 does not encompass a lipid vesicle.

In view of the foregoing, it is submitted that nothing in Navarro et al. and Weiner et al., taken alone or together, renders the claimed invention obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 1-4, 6, 8, 12-13, 15-16, 19-21, 23-24, 26, 29, 112, 118-125, 128, 131-132, and 135-138.

VI. At page 11 of the Official Action, claims 14, 30-33, 36-44, and 133 have been rejected under 35 USC § 103 (a), as being unpatentable over Navarro et al. in view of Weiner et al. and further in view of Wong et al.

The Examiner asserts that it would have been obvious to the skilled artisan to combine the teachings of the references and further utilize a propellant because "Wong et al. teaches that a propellant allows a solution to aerosolize." The Examiner further asserts that "it would have been obvious to use either propylene glycol or glycerol and arrive at the instant invention."

In view of the remarks set forth herein, this rejection is respectfully traversed. Claims 41-42 have been canceled without prejudice or disclaimer, rendering this rejection moot with respect to these claims.

As discussed above, Applicants submit that a proper case of *prima facie* obviousness has not been established because there is no motivation to modify Navarro et al. to incorporate the minoxidil acid salt of Weiner et al. Please *see* the discussions set forth above in Sections I and V regarding each of Navarro et al. and Weiner et al., which are hereby incorporated herein by reference in their entirety. *See also* the Abram Declaration.

Applicants submit that Wong et al. does not cure the deficiencies of Navarro et al. and Weiner et al. because Wong et al. also does not teach or suggest employing a minoxidil acid salt.

In view of the foregoing, it is submitted that nothing in Navarro et al., Weiner et al., and Wong et al., taken alone or together, renders the claimed invention obvious within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection of pending claims 14, 30-33, 36-40, 43-44, and 133.

VII. At page 11 of the Official Action, claims 112, 118-119, 121-128, 131-132, and 135-138 have been rejected under 35 USC § 103 (a), as being unpatentable over Bazzano in view of Weiner et al. or Yu et al.

The Examiner asserts that it would have been obvious to the skilled artisan to combine the teachings of Bazzano and Weiner et al. and utilize the instant minoxidil acid salt. Alternatively, the Examiner asserts that it would have been obvious to combine the teachings of Bazzano and Yu et al. and utilize the instant acid because Yu et al. teaches adding lactic acid dissolves minoxidil providing better penetration of minoxidil into the hair follicle.

The Examiner further asserts that independent claim 112 includes a penetration agent and that retinoic acid reads on a "penetrating agent."

In view of the remarks set forth herein, this rejection is traversed. Claims 126-127 have been canceled without prejudice or disclaimer, rendering this rejection moot with respect to these claims.

With regard to the rejection of the claims as obvious over Bazzano in view of Weiner et al. or Yu et al., it is submitted that a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Bazzano to incorporate the minoxidil acid salt of Weiner et al. or Yu et al. Please *see* the above remarks in Sections I-VI regarding each of Weiner et al. and Yu et al., which are incorporated herein by reference in their entirety.

Claim 113 has been canceled without prejudice or disclaimer. Claim 112 has been amended to include the limitations of canceled claim 113 requiring

specific penetration enhancers. Accordingly, claim 112 does not encompass retinoic acid, as alleged by the Examiner, and thus falls outside the scope of the Bazzano reference.

In view of the foregoing, it is submitted that nothing in any of the applied references, taken alone or together, suggest the subject matter of claims 112, 118-119, 121-126, 128, 131-132, and 135-138, within the meaning of 35 USC § 103. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

VIII. At page 14 of the final Official Action, claims 1-4, 6, 8, 12-16, 19-21, 23-24, 26-33, 36-44, 112-114, 119-128, 131-133, and 135-138 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 21-24 and 26-29 of co-pending Application No. 10/949,116.

The Examiner asserts that although the claims are not identical, they are not patentably distinct from each other since the subject matter claimed in both applications is similar. The Examiner acknowledges that Terminal Disclaimers were filed on October 30, 2006, but that the rejection is maintained until the Terminal Disclaimers have been reviewed and accepted.

Applicants note that the Terminal Disclaimers were approved on November 14, 2006, as indicated in United States Patent and Trademark Office Internal Document DISQ. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

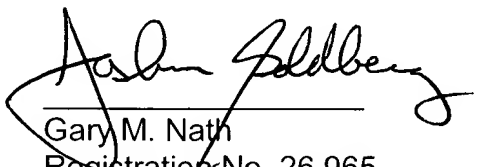
CONCLUSION

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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